

Antiseizure Effects with Selective TARPy8 Negative Allosteric Modulators in Preclinical Seizure Models

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Background

• AMPA receptors (AMPARs) are a clinically validated therapeutic target for epilepsy

- Broad AMPAR inhibition is associated with undesirable hindbrain-related adverse events (AEs) such as somnolence and gait disturbance²
- Transmembrane AMPAR regulatory proteins (TARPs) are anatomically specific mediators of AMPAR trafficking, subcellular localization, and gating; TARPy8 is enriched in regions associated with seizures with little to no expression in the hindbrain^{3,4}
- RAP-219 is a potent, selective AMPAR/TARPγ8 negative allosteric modulator (NAM) offering neuroanatomically specific AMPAR modulation for the treatment of seizures

Objectives

• To examine the efficacy and tolerability of RAP-219 in established preclinical seizure models

• To examine toleration of seizure protection after chronic dosing of a RAP-219 analog, RTX-1738

Methods

Table 1. Seizure Threshold and Protection Tested in Adult Male CF-1a Mice

Model	Treatment Groups	Test	Outcome	Endpoint
PTZ	 RAP-219: single dose, p.o. Vehicle: single dose 	PTZ infusion	Seizure threshold	Time to first twitch and to onset of sustained clonus ^b
CK	 RAP-219: single dose, p.o. RTX-1738: single dose and 7 d QD°, p.o. Vehicle: single dose and 7 d QD° 	Corneal stimulation challenge	Seizure protection	• Racine scale score ⁵
		Rotarod test	Motoric impairment	 Number of falls during 1-min period
		Open-field test	Locomotor activity	Total distance traveledHorizontal/vertical activity count

^aCharles River, Portage, MI.; ^bED₅₀ values: group means for twitch and clonus compared using ANOVA, followed by Dunnett's post-hoc analysis;

PTZ RAP-219 doses: 0.01, 0.1, and 1 mg/kg; CK RAP-219 doses: 0.01, 0.02, 0.03, 1, and 3mg/kg; RTX-1738 doses: 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg; Phenotypic secondarily generalized seizures at Racine scale score of 5. CK – corneal kindling; PTZ – pentylenetetrazol; QD – once daily.

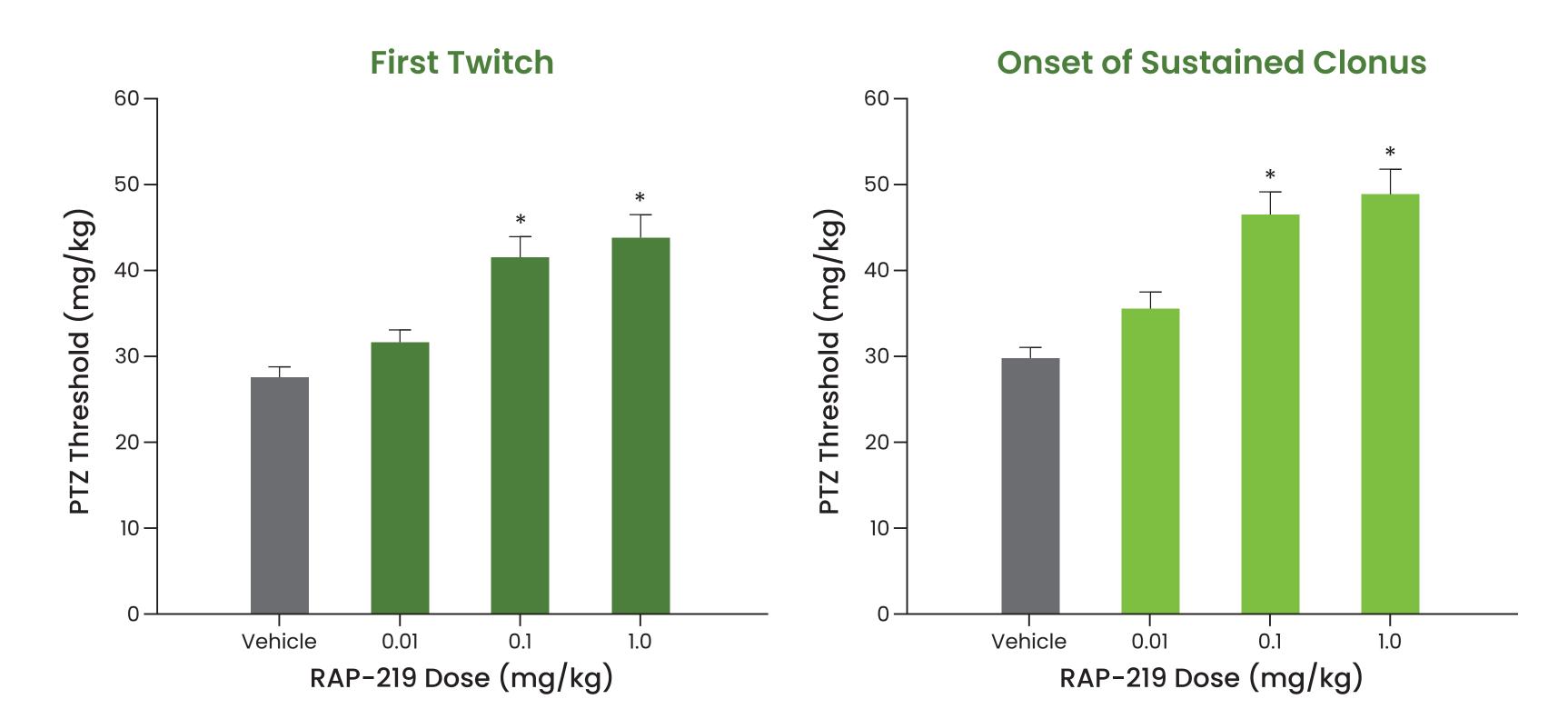
- Efficacy was plotted as a function of the mean plasma concentration (Cp) determined by pharmacokinetic (PK) analysis in naïve mice
- Data were fitted to Hill functions to estimate ED₅₀ and plasma EC₅₀
- Receptor occupancy (RO) as a function of Cp in rat (ex vivo autoradiography) was analyzed to demonstrate the correspondence of the CK efficacy and RO as a function of Cp

Results

RAP-219 treatment raised the seizure threshold and provided seizure protection

• Compared to vehicle, RAP-219 at 0.1 and 1 mg/kg was associated with a significantly higher threshold to both first twitch and onset of sustained clonus in the pentylenetetrazol (PTZ) model (P<0.01)

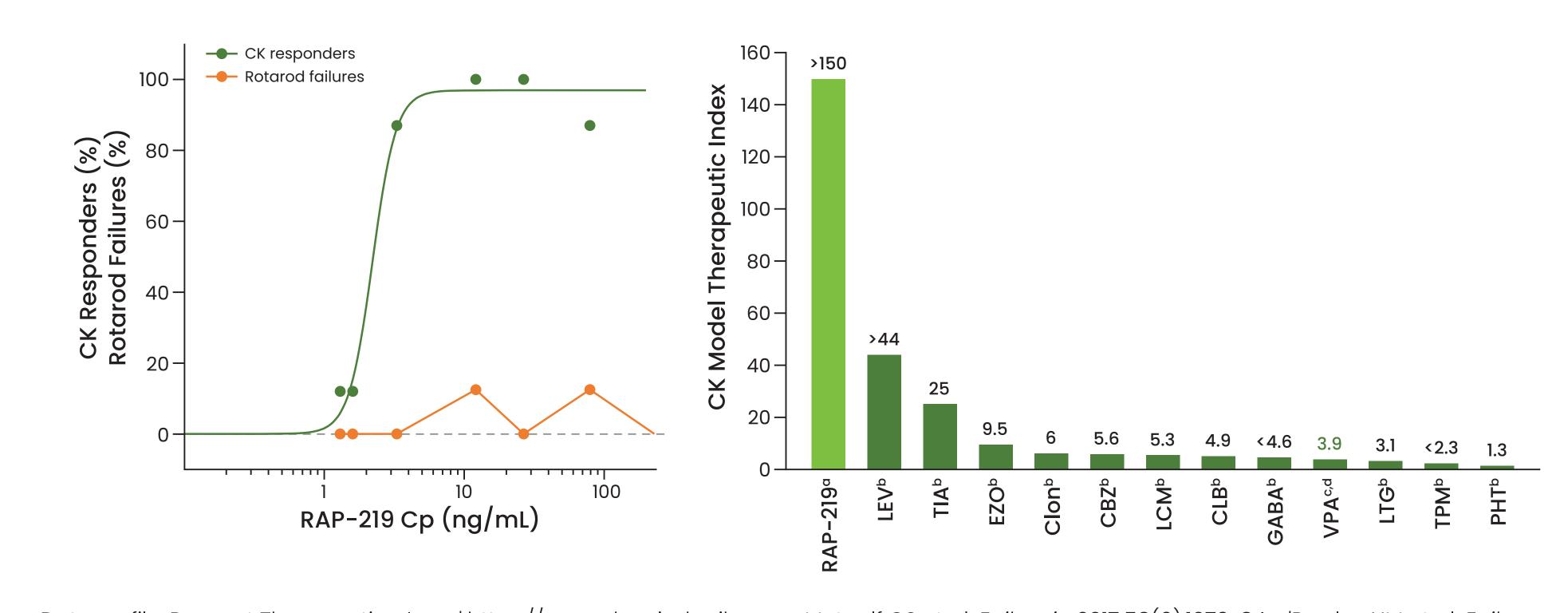
Figure 1. Significant, Dose-Dependent Increase in Seizure Threshold to First Twitch and Onset of Sustained Clonus



First twitch: $ED_{50} = 0.02 \text{ mg/kg}$; $EC_{50} = 2.9 \text{ ng/mL}$; Onset of sustained clonus: $ED_{50} = 0.02 \text{ mg/kg}$; $EC_{50} = 2.4 \text{ ng/mL}$; $EC_{50} = 2.4 \text{ ng/mL}$; $EC_{50} = 2.9 \text{ ng/mL}$; $EC_$ a corresponding plasma EC₅₀ of 2.3 ng/mL. PTZ – pentylenetetrazol.

Percentage of responders in the CK model increased with RAP-219 dose

Figure 2. High Therapeutic Index as Assessed by Dose-Dependent Seizure Protection Without Motoric Impairment in the CK Model

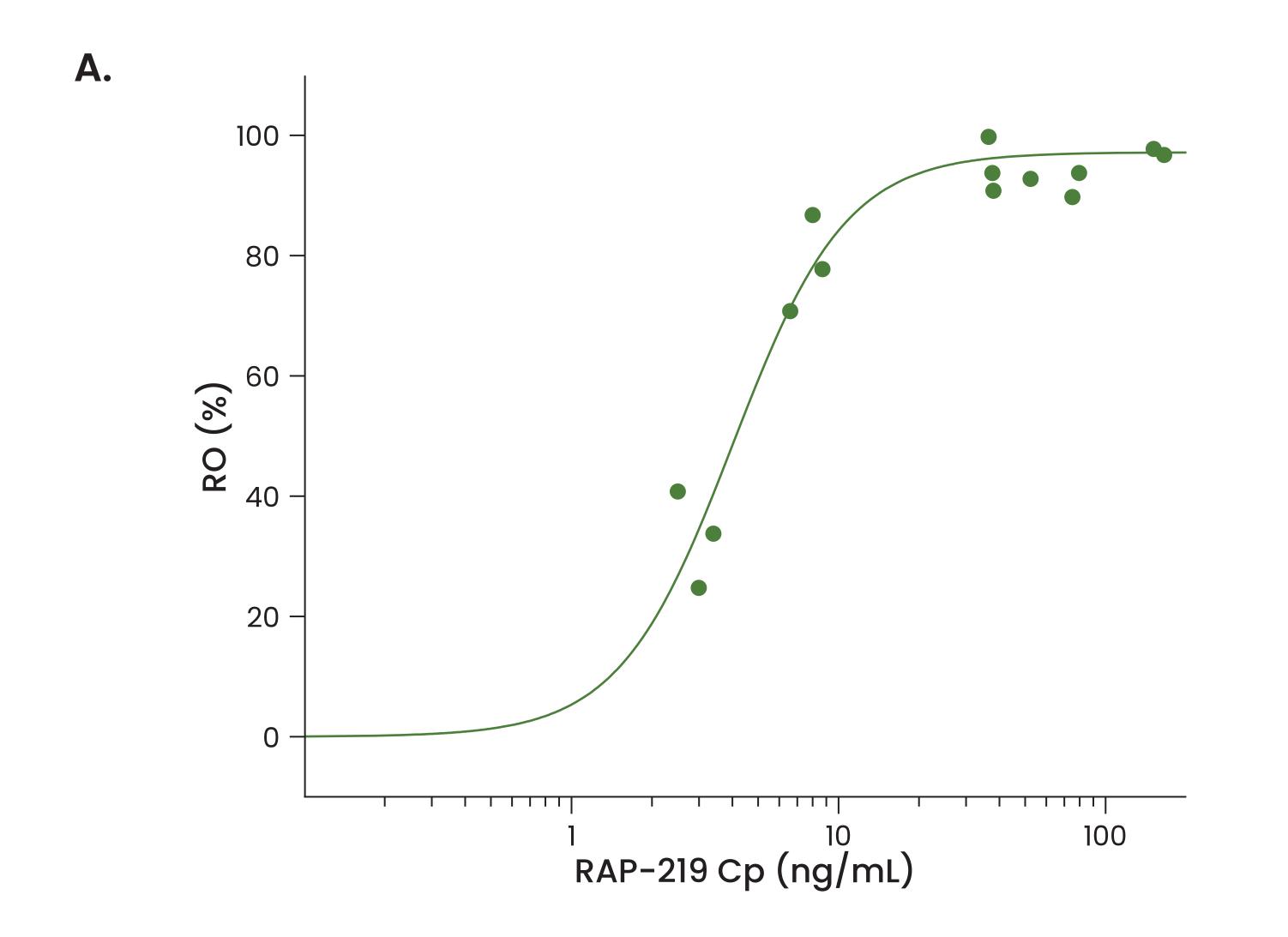


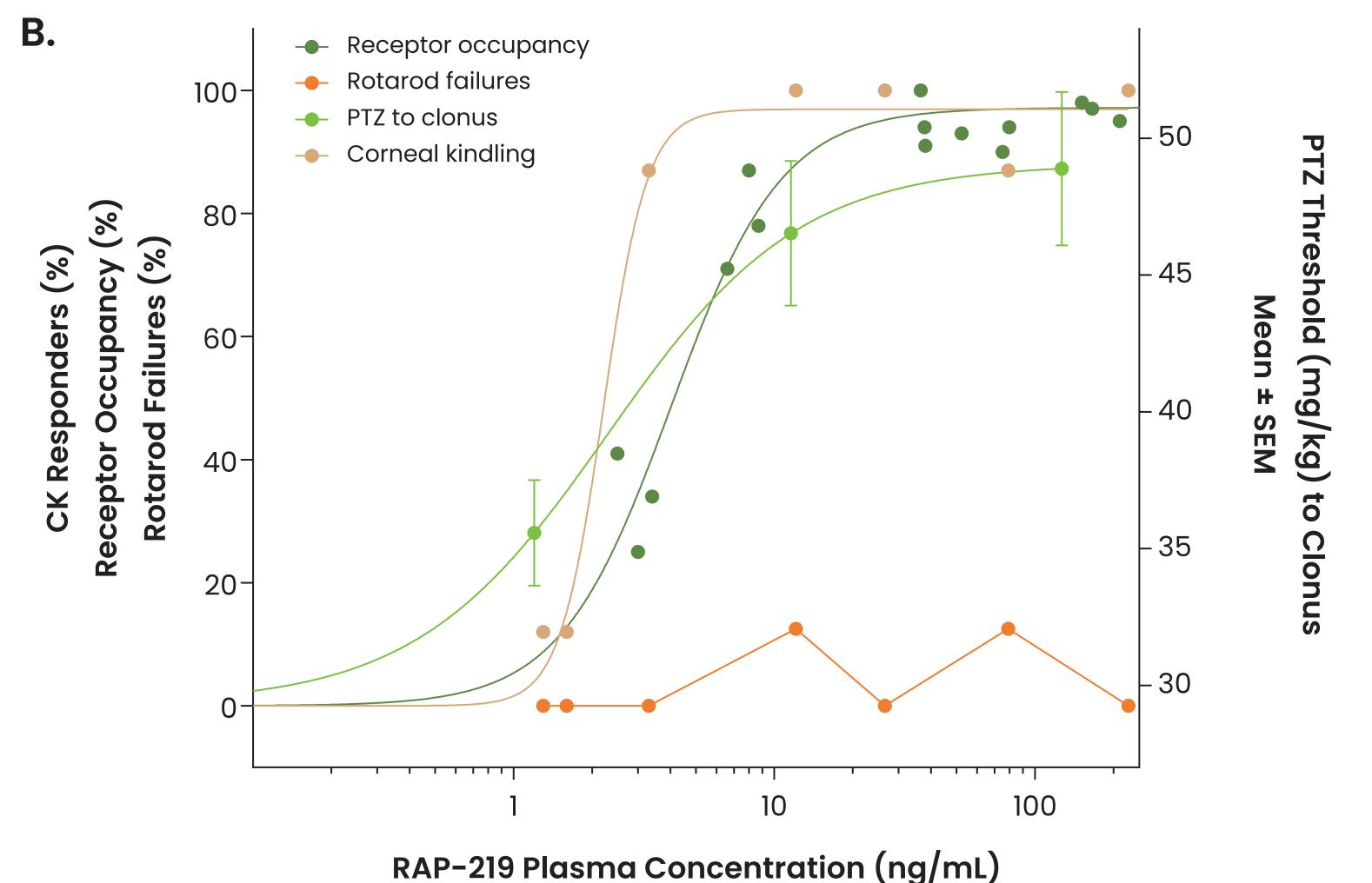
Data on file, Rapport Therapeutics, Inc.; https://panache.ninds.nih.gov; Metcalf CS et al. Epilepsia 2017;58(6):1073-84; Rowley NM et al. Epilepsy Res. 2010;92(2-3):163-9 CBZ – carbamazepine; CLB – clobazam; CK – corneal kindling; Clon – clonazepam; EZO – ezogabine; GABA – gabapentin; LCM – lacosamide; LTG – lamotrigine; LEV – levetiracetam; PHT – phenytoin; TIA – tiagabine; TPM – topiramate; VPA – valproate.

Acknowledgments

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Figure 3. A. RAP-219 RO EC₅₀ of 3.3 ng/mL Cp in Rat (4 h) and **B.** Maximal Protection With RAP-219 at Predicted Human RO (~70% RO and Corresponding $Cp \sim 7 ng/mL$





CK – corneal kindling; Cp – plasma concentration; QD – once daily; RO – receptor occupancy.

The authors thank Michael Ameriks and Brian Lord of Johnson & Johnson Innovative Medicine for his work with RAP-219, H.

Steve White and Cameron Metcalf of NeuroAdjuvants, Inc., for performing the anticonvulsant studies for RAP-219 and Karen

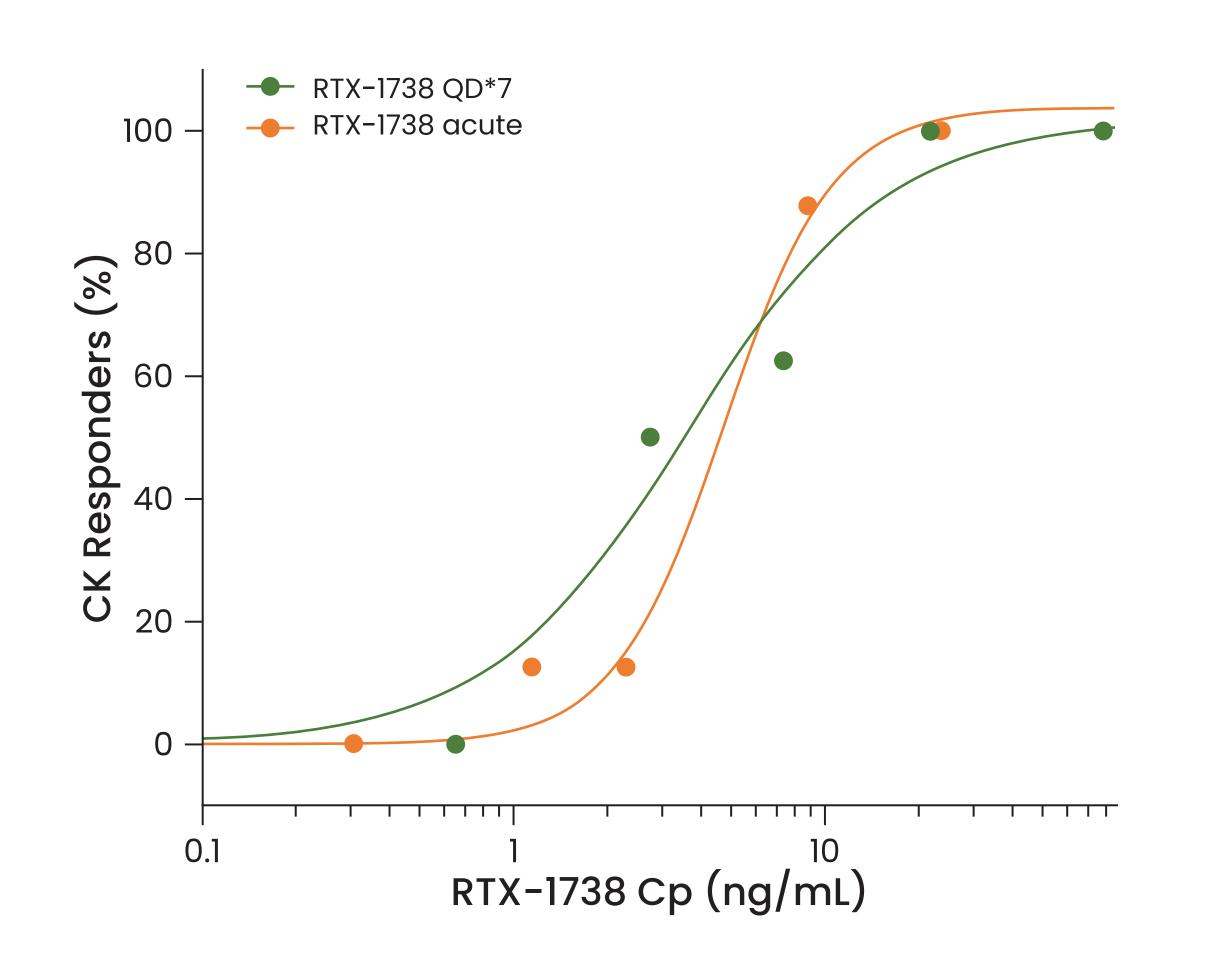
S. Wilcox of Anticonvulsant Drug Development for performing the anticonvulsant studies for RTX-1738. The authors also thank

Mari Willeman, PhD, and Anthony DiLauro, PhD, of PharmaWrite, LLC, for writing and editorial assistance, which were funded by

RTX-1738 RO EC₅₀ value of 3.2 ng/mL

• No differences in locomotor activity were observed between vehicle and any RTX-1738 dose

Figure 4. Efficacy of RAP-219 Analog, RTX-1738, Remains Similar in CK Model Over 7 Days



Maximal protection was observed for RTX-1738 with RO ~90%, and Cp ~10 ng/mL; Acute: ED₅₀ of 0.05 mg/kg with a corresponding plasma EC₅₀ of 4.7 ng/mL; Chronic: ED₅₀ of 0.01 mg/kg and a corresponding plasma EC₅₀ of 3.6 ng/mL.

CK – corneal kindling; Cp – plasma concentration; QD – once daily; RO – receptor occupancy.

Conclusions

- RAP-219, a novel and selective AMPAR/TARPγ8 NAM currently in Phase 2 development for the treatment of focal and generalized seizures, provided potent, dosedependent antiseizure effects in both the PTZ and CK preclinical seizure models
- Maximal protection was observed with 70% RO and RAP-219 Cp of 7 ng/mL
- Antiseizure effects were maintained over 7-day QD oral dosing with a RAP-219 analog
- Exposures that produced antiseizure effects did not impair motor function, yielding a high therapeutic index
- These results are consistent with targeted inhibition of AMPARs based on the neurospecificity of TARPγ8 expression (hippocampus, cortex, amygdala) while avoiding AEs associated with hindbrain AMPAR inhibition such as somnolence, motoric impairment, and falls



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Disclosures

JAM, BS, LV, DB: Rapport Therapeutics, Inc.: employee and stock ownership. MPM: Johnson & Johnson Innovative Medicine: employee and stock ownership.





